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Generalized Born and Nonpolar Models in Solvation Free Energies.

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Studies of biomolecular systems at a mesoscopic level require knowledge of effective, mezoscopic interaction potentials. Such potentials are being developed, accounting for continuum models of solvent. One of the approaches is a mean-field electrostatic Generalized Born (GB) model. For review of mezoscopic models and theories, see[1]. The GB model and methods of computing GB radii are briefly presented, together with an outline of an SCC-DFTB method and CM3 SCC-DFTB charges[2]. These charges were specifically designed to provide high quality description of electrostatic properties on a basis of the approximate density functional theory calculations. Differences between the experimental solvation energies and the GB electrostatic energies to the solvation energies give nonpolar (hydrophobic) contributions. The hydrophobic energies were fitted to solvent accessible surface area as well as to a polynomial series depending of the Born radii. Both approaches give satisfactory results, however, the latter is faster. Our model was tested using a set of experimental hydration energies for simple molecules[3]. Analytical approximations of the nonpolar contribution to the mezoscopic interaction potentials (hydrophobic contribution to the free energy of solvation) are proposed.

1 Introduction

The purpose of our study is to design fast, mesoscopic molecular interaction potentials, which are capable of reproducing solvation free energies. The electrostatic part of the free energy of solvation is approximated with the Generalized Born (GB) model using the CM3/SCC-DFTB atomic charges[2] as the source of the original electrostatic field.

2 Class IV charges

In brief, CM3/SCC-DFTB charges are given by the formula:

$$q_k = q_k^0 + \sum_{k' \neq k} T_{kk'}(B_{kk'}) = q_k^0 + \sum_{k' \neq k} D_{Z_k Z_{k'}} B_{kk'} + C_{Z_k Z_{k'}} (B_{kk'})^2 \qquad (1)$$

where q_k^0 are typical Mulliken charges, and $T_{kk'}$ is a quadratic function of Mayer's bond orders $B_{kk'}$. The method for calculating CM3/SCC-DFTB charges was described in detail elsewhere[2].

3 Free energy of solvation

The solvation free energy G_{solv} can be decomposed into an effective electrostatic energy G_B, a nonpolar (hydrophobic) part G_{np} and a cross term G_{cross}, which typically is neglected. We use the Generalized Born Model (GB)[4] to represent the electrostatic part.

$$G_B = -\frac{1}{2}\left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{ex}}\right)\sum_{k,l}\frac{q_k q_l}{\sqrt{r_{kl}^2 + R_k R_l e^{-\frac{r_{kl}^2}{4R_k R_l}}}} \tag{2}$$

where r_{kl} is the distance between atoms, ϵ_{in}, ϵ_{ex} are the dielectric constants of interior and exterior of the molecule, respectively. q_k, q_l are the atomic charges. R_k is an effective Born radius. The exact electrostatic energy, U^k_{single}, of a model molecule containing a single charge on the atom k is:

$$U^k_{single} = -\frac{1}{2}\left(\frac{1}{\epsilon_{in}} - \frac{1}{\epsilon_{ex}}\right)\frac{q_k^2}{R_k} \tag{3}$$

A nonpolar contribution to the solvation free energy, G_{np}, is usually approximated using solvent accessible surface area (SASA). One of such methods, that bears similarity to our approach, is a Surface Generalized Born – Nonpolar model[5], in which the nonpolar component (G_{np}) is described as a polynomial of A_i, where A_i is the SASA of the atom i.

$$G_{np} = \sum_{i=1}^{N}\left(\gamma(k_i)A_i + \alpha(k_i)\right) \tag{4}$$

$\gamma(k_i)$ parameters are interpreted as a surface tension coefficients, and $\alpha(k_i)$ are adjustable parameters dependent on atom types (k_i).

4 Numerical implementation and results

Born radius of an atom in a molecule contains a qualitative information of how deeply the atom is buried inside the molecule. Taking advantage of this fact, in our approach we use polynomials the inverse of R_k, instead of using A_i. Coefficients of these polynomials depend on the atom types Z_k.

$$G_{np} = \sum_k\left(a_{1,Z_k}\frac{1}{R_k} + a_{0,Z_k}\right) \tag{5}$$

Since the cross term is neglected in our model, $G_{np} = G_{solv} - G_B = G_{exp} - G_B$, an estimate of the nonpolar contributions to the free energy of solvation G_{solv} can be computed by subtracting the electrostatic contributions from the experimental values of the free energy of solvation. These approximate values of the nonpolar terms were used for parameterization of our model. It was carried out using a set of more than one hundred molecules selected from[3]. For each molecule CM3/SCC-DFTB charges were computed and used to estimate the GB energies. At the same time, electrostatic contribution was calculated by solving the Poisson-Boltzmann equation, and removing the Coulomb part of the energy. Accuracy of the GB approximation was validated by comparison with the PB results, see Figure 1. Coefficients in equation 5 were chosen to yield an optimal fit. Resulting nonpolar energies against the experimental estimates are presented in Figure 2.

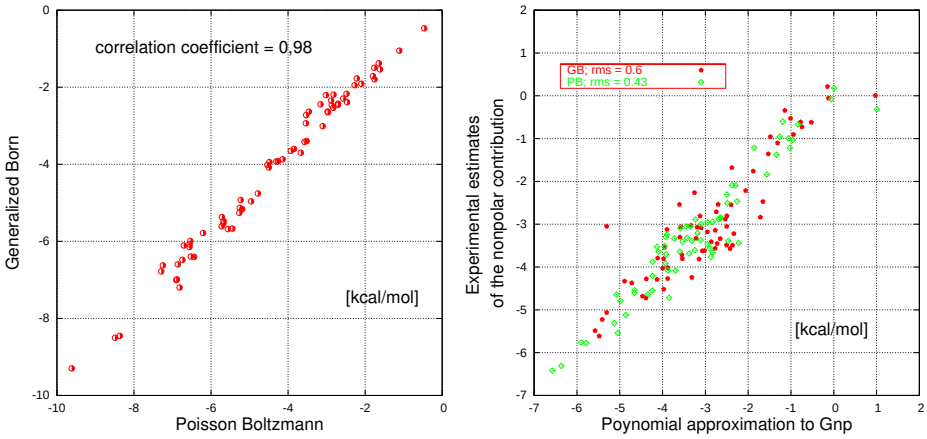

Figure 1. Electrostatic contribution to the free energy of solvation (left). Nonpolar contribution to the free energy of solvation (right).

5 Concluding remarks

Fitting the nonpolar term G_{np} to reproduce the free energies of solvation was the main goal of this work. We proposed a fast and simple model. Our results suggest it is sufficient to account only for the first order polynomials.

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